

Award Number:

W81XWH-11-2-0148

TITLE:

National Biocontainment Training Center

PRINCIPAL INVESTIGATOR:

James LeDuc, PhD

CONTRACTING ORGANIZATION:

University of Texas Medical Branch at Galveston  
Galveston, TX 77555-5302

REPORT DATE:

July 2013

TYPE OF REPORT:

Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command  
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT:

Approved for public release; distribution unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

# REPORT DOCUMENTATION PAGE

*Form Approved  
OMB No. 0704-0188*

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. **PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.**

<b>1. REPORT DATE (DD-MM-YYYY)</b> August 2013		<b>2. REPORT TYPE</b> Annual		<b>3. DATES COVERED (From - To)</b> 15-July-2012 to 14-July-2013	
<b>4. TITLE AND SUBTITLE</b> National Biocontainment Training Center				<b>5a. CONTRACT NUMBER</b> W81XWH-11-2-0148	
				<b>5b. GRANT NUMBER</b> W81XWH-11-2-0148	
				<b>5c. PROGRAM ELEMENT NUMBER</b>	
<b>6. AUTHOR(S)</b> LeDuc, James Ksiazek, Thomas				<b>5d. PROJECT NUMBER</b>	
				<b>5e. TASK NUMBER</b>	
				<b>5f. WORK UNIT NUMBER</b>	
<b>7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)</b>  University of Texas Medical Branch at Galveston  Galveston, TX 77555-5302				<b>8. PERFORMING ORGANIZATION REPORT NUMBER</b>	
<b>9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)</b> USA Med Research Acq Activity 820 Chandler St Fort Detrick, MD 21702-5014				<b>10. SPONSOR/MONITOR'S ACRONYM(S)</b>	
				<b>11. SPONSOR/MONITOR'S REPORT NUMBER(S)</b>	
<b>12. DISTRIBUTION / AVAILABILITY STATEMENT</b>  Approved for public release; distribution unlimited					
<b>13. SUPPLEMENTARY NOTES</b>					
<b>14. ABSTRACT</b> Scientific investigations, product development, and response to threats of endemic diseases and emerging pathogens are undertaken to reduce the risk of infection and lessen the impact of naturally occurring or man-made pathogens to humankind. If, however, proper precautions are not taken and safe practices are not utilized there is a risk that these interventions could contribute to increase the potential exposure of individual scientists and technical staff, as well as surrounding communities, to dangerous infectious diseases. The threat is perhaps greatest within the international laboratory community where these dangerous pathogens are routinely manipulated and investigated. This award supports critical training and hands-on experience to predominantly international scientists working with especially dangerous pathogens that require special biocontainment facilities for their safe and secure handling.					
<b>15. SUBJECT TERMS</b> ^~^æÃ*ã~{leftrightarrow;äääÃ					
<b>16. SECURITY CLASSIFICATION OF:</b>		<b>17. LIMITATION OF ABSTRACT</b>	<b>18. NUMBER OF PAGES</b>	<b>19a. NAME OF RESPONSIBLE PERSON</b> USAMRMC	
<b>a. REPORT</b>	<b>b. ABSTRACT</b>	<b>c. THIS PAGE</b>	SAR	32	<b>19b. TELEPHONE NUMBER</b> (include area code)

**W81XWH-11-2-0148 (NBTC2) Annual Report July 2012 – July 2013**

<b>Introduction</b>	<b>2</b>
<b>Body</b>	<b>3-29</b>
<b>Staffing Report</b>	<b>3-4</b>
<b>Specific Aims</b>	
<b>Aim 1</b>	<b>4-14</b>
<b>Aim 2</b>	<b>14-20</b>
<b>Aim 3</b>	<b>20-24</b>
<b>Aim 4</b>	<b>24-25</b>
<b>Aim 5</b>	<b>25-29</b>
<b>Key Research Accomplishments</b>	<b>30</b>
<b>Reportable Outcomes</b>	<b>30</b>
<b>Conclusions</b>	<b>30</b>

## **INTRODUCTION.**

Scientific investigations, product development, and response to threats of endemic diseases and emerging pathogens are all undertaken in modern research biocontainment laboratories to reduce the risk of infection and lessen the impact of naturally occurring or man-made pathogens to humankind. There is, however, a risk that these activities could contribute to increase the potential exposure of individual scientists and technical staff, as well as surrounding communities, to dangerous infectious diseases if proper precautions are not taken and safe practices are not utilized in laboratories where this work is undertaken.

The threat is perhaps greatest within the international laboratory community where these dangerous pathogens may exist in nature and may be routinely manipulated and investigated in laboratories under less than ideal conditions by individuals who may lack adequate training or experience. Historically, this work was concentrated in a few research or governmental facilities where appropriate biocontainment existed and where a limited number of highly trained investigators conducted the research. Today, the investigation of emerging infectious diseases, the development of novel products to diagnose these infections, prevent infection and treat those who have become ill, has become a global enterprise. Unfortunately, some of the individuals and their parent organizations attempting to conduct this work do not have in place adequate facilities, training or administrative oversight to ensure that this important research and development is undertaken in the safest possible fashion, or that the products under development are evaluated safely.

Through the aims identified below, we are sharing the experiences gained as we operate the unique facilities of the Galveston National Laboratory (GNL) with others involved in laboratory research. Our experiences and lessons learned in the administration, investigation and effort to develop formal regulated studies were gained from years of biocontainment laboratory operations and from training the scientists who work within them. This unique and valuable experience is being shared with other biocontainment laboratory scientists and program directors around the world through the National Biocontainment Training Center's (NBTC) expanded scope of work.

The progress reported here complements activities summarized separately in a companion project (Award Number W81XWH-09-2-0053, also titled National Biocontainment Training Center). Together these awards support a coordinated effort to provide critical training and hands-on experience to U.S. national and international scientists working with especially dangerous pathogens that require special biocontainment facilities for their safe and secure handling.

## **BODY.**

Research accomplishments associated with each specific aim are summarized below. This annual report covers July 2012 – July 2013.

### ***Staffing Report.***

**James W. LeDuc** serves as principal investigator for the training center and is responsible for oversight of program initiatives, fiscal management and progress reporting.

**Christopher Gibbs** assists in the training of building engineering fellows and provides hands-on guidance, especially in the care, maintenance and certification of the biological safety cabinets used in virtually every laboratory that handles pathogens.

**Miguel Grimaldo** directs the building engineering fellowship and provides lectures and hands-on guidance to fellows within the program. He also represents the program at meetings and events dedicated to biocontainment engineering.

**Aaron Miller** assists with the efforts to address Aim 4, to develop and implement training opportunities that focus on the safe and secure operations of novel laboratory instrumentation being introduced into the biocontainment laboratory environment.

**John Morrill** provides assistance in the training of students in the care, use and handling of laboratory animals within BSL-3 and BSL-4 biocontainment laboratories.

**Alisha Prather** assists in the preparation of reports, in the organization and implementation of guest lectures and with general communications of program activities. She also monitors relevant policy issues related to international biosafety and biosecurity.

**Ronald Veselenak** works with Aaron Miller to address Aim 4, to develop and implement training opportunities that focus on the safe and secure operations of novel laboratory instrumentation being introduced into the biocontainment laboratory environment.

**Leoncio Vergara** provides students with technical assistance and training in the safe and secure use of the modern imaging equipment found in the GNL biocontainment laboratories.

**Sheri Leavitt** assists senior trainers with the training of students specializing in in-vivo techniques.

**Mary Milazzo** assists in the mentored training of students and staff in the BSL4 biocontainment laboratory. She also assists in the administration of tracking and mentored training and the status of approved users in the BSL4 containment laboratories.

**Victoria Ramirez** serves as the senior administrative support associate for the NBTC and is involved in center outreach programs as well as with the trainee registration process for all external participants, nationally and internationally.

**Nathaniel Schueller** assists senior trainers with the training of students specializing in in-vivo techniques.

### ***Specific Aims***

***Aim 1. To provide standards-based biological containment laboratory safety knowledge to international partners.***

**Background:** There is a massive unmet need for training in biosafety and biosecurity on an international level, which could ultimately impact national security. To address this need we are expanding our efforts to engage international partners in an educational program that is structured around the same principles and practices as those currently in use within our existing funded NBTC, but focused on trainees from international centers possessing a biocontainment facility involved in the diagnosis, research and development, or the clinical care of patients suffering from especially dangerous infectious diseases. We strive to provide on-site training so that the instruction is tailored to meet the local facility and environmental needs and capacity of the end users. We focus on opportunities to “train the trainer” so that our efforts may be multiplied within that country. There is a fledgling network of national and regional organizations that are focused on biosafety, biosecurity and related fields of interest, and we are working with these organizations, and other professional groups to help build this network and further enhance this important aspect of research and development as it relates to infectious diseases.

### **Progress:**

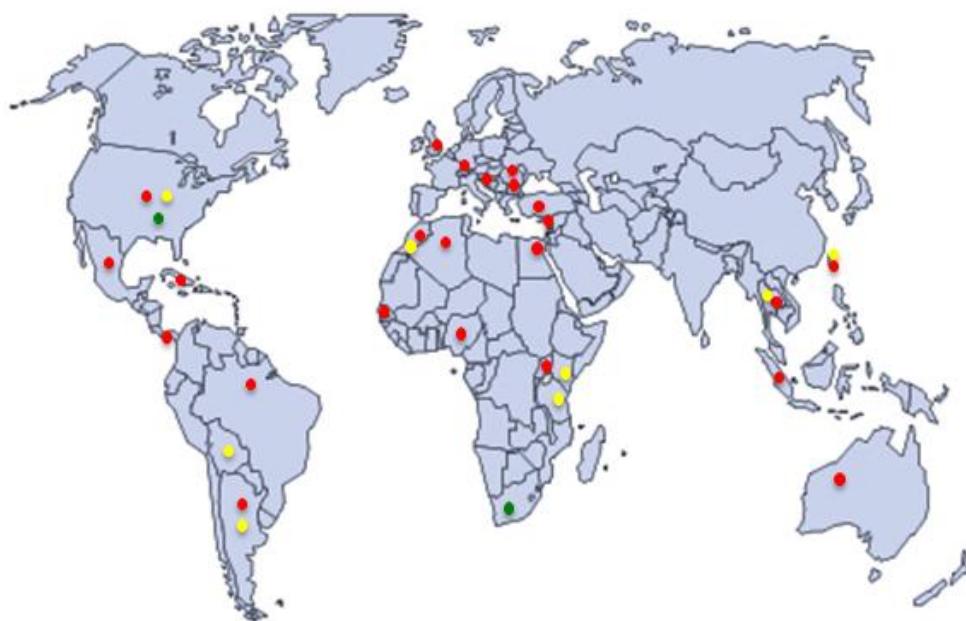
The world map on the following page reflects the international locations from which and/or to which NBTC trainees and trainers have travelled since the inception of the biosafety training program in an effort to train laboratorians in the proper procedures for their research.

## International Training 2006 – July 2013

### **BSL2-BSL3-ABSL3-BSL4**

#### **Training**

Algeria  
Argentina  
Australia  
Brazil  
Bolivia  
Bulgaria  
Cameroon  
Cuba  
Egypt  
Hawaii  
Israel  
Kenya  
Mexico  
Morocco  
Panama  
Romania  
Senegal  
Singapore  
Slovenia  
Tanzania  
Turkey  
Swiss  
Taiwan  
Thailand  
Uganda  
UK  
USA



- ● UTMB traveled for training
- ● Traveled to UTMB for training
- ● Pre-conference course training- ABSA-AfBSA

Progress during this past reporting year on Aim 1, highlighted by quarter (Q1, Q2, Q3, Q4) includes:

#### **Q1 highlights –**

- **Koc University in Istanbul, Turkey.** Two students from Koc University in Istanbul, Turkey came to the NBTC for onsite laboratory biosafety training. These student researchers work at the same institution as one of our NBTC fellows, Dr. Aysen Gargili. The researchers were with us for two weeks and took both the BSL3 and ABSL3 courses.
- **Instituto Nacional de Enfermedades Virales Humanas, Argentina.** We also trained nine individuals from the Instituto Nacional de Enfermedades Virales Humanas (INEVH), Argentina at BSL3 and sixteen individuals in BSL2 theory. Training was offered on site in the INEVH biocontainment laboratories in Pergamino, Argentina. By providing training on site in their own familiar laboratory setting, the students are better able to assimilate improved practices

and procedures into their daily routine.

- **Centro Nacional de enfermedades tropicales (CENETROP) in Bolivia.**

Following this training and due to collaborations between UTMB researcher Dr. Aguilar and members of INEVH, NBTC trainers were asked to travel to Centro Nacional de enfermedades tropicales (CENETROP) in Bolivia to train new BSL3 researchers in preparation of the opening of their BSL3 facility. This course was organized by Pan American Health Organization (PAHO). Two



consultants from the NBTC travelled to Bolivia to provide theoretical and practical training for staff who will work in the national laboratory in Santa Cruz (*pictured above, August 2012*). Six researchers participated in our BSL3 course and 11 participated in theoretical BSL3 training. The director, manager, researchers, and staff were trained in biological safety techniques critical for functional operation in a BSL3 environment. The participants were very engaged throughout the training often asking questions and posing scenarios. Evidence of achievement by the trainees was demonstrated in successful completion of theoretical and practical assessments. All participants were awarded certificates. In addition, local administrators have been in contact with the NBTC about possible future training sessions for a broader laboratory audience in Santa Cruz.

- **International Federation of Biosafety Associations.** Mr. Miguel Grimaldo, the Galveston National Laboratory biocontainment engineer with the training center, participated as a member of the Biocontainment Engineering Working Group of the International Federation of Biosafety Associations (IFBA). One of the goals of the Working Group is to develop risk-management based guidelines for biocontainment laboratories that will eventually be endorsed by international organizations such as World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO) and the Office International des Epizooties (OIE) the World Organization for Animal Health.

- **European Research Infrastructure on Highly Pathogenic Agents project.** Mr. Grimaldo was also invited to the workshop of the European Research Infrastructure on Highly Pathogenic Agents (ERINHA) project. This activity was an international expert workshop on the evidence-based design on high containment facilities. It was held in London between 25th and 27th of September 2012. Mr. Grimaldo presented an overview on BSL4 Ventilation - Design and Operation. This invitation-only workshop was attended by an international audience of containment experts (facility managers, scientists, architects and engineers) from France,

Germany, Italy, Netherlands, Australia, Austria, United Kingdom, Slovakia, Denmark, Greece, Romania, Spain, Portugal, Canada and the U.S.

## Q2 highlights –

- **AFRIMS, Bangkok, Thailand.**  
NBTC trainers Jason Hardcastle and Vickie Jones travelled to Thailand at the end of November 2012 to present a two-week BSL3 course offered to the USAMRMC - AFRIMS (U.S. Army Medical Research and Material Command - Armed Forces Research Institute of Medical Sciences, a U.S. Department of Defense overseas facility) research staff. Simultaneously NBTC trainer Belinda Rivera and GNL biocontainment veterinarian Dr. Curtis Klages travelled with them the first week to offer presentations to a different set of individuals on Non-Human Primate and ABSL3 training. This was in follow-up to training we offered at UTMB to three members of their staff in early 2012. An update on this training in Thailand follows: Members of the AFRIMS invited NBTC trainers to Bangkok, Thailand to offer BSL3, ABSL3 and NHP training to researchers stationed at their facilities in the region. AFRIMS is home to over 300 staff members who are a highly integrated group of U.S. and Thai military and civilians from both countries. The U.S. Component Commander is on the U.S. Ambassador's Country Team for Thailand and provides advice to the country team on biomedical issues. At



AFRIMS, twenty researchers participated in our BSL3 course and 28 participated in theoretical BSL3 training. The Institute's director, manager, researchers, and staff were trained in biological safety techniques critical for functional operation in a BSL3 environment. The participants were very engaged throughout the training, often asking questions and posing laboratory scenarios. Evidence of achievement by the trainees was demonstrated in successful completion of theoretical and practical assessments. All participants (*pictured previous page, top right*) were awarded certificates. Four participants (*pictured previous page, middle right*) completed the ABSL3 training and ten staff participated in the theoretical class. Seven participants completed the NHP training and 11 participated in the theoretical class (*pictured previous page, bottom right*). The veterinarians and staff were trained in biological and animal safety techniques critical for functional operation in their containment animal facilities.

- **Southern Africa Centre for Infectious Diseases Surveillance (SACIDS), Tanzania.**

Following the African Biological Safety Association (AfBSA) meeting in Johannesburg in the summer of 2012, the NBTC was asked to offer BSL2 theoretical training to several institutions from East Africa. A consultant from NBTC was invited to Tanzania to provide



theoretical training for 11 staff working in laboratories in Tanzania, Democratic Republic of Congo (DRC), Mozambique, South Africa, Zambia as part of the Southern African Centre for Infectious Diseases Surveillance (SACIDS). SACIDS is a One Health consortium of southern African medical and veterinary, academic and research institutions involved with infectious diseases of humans and animals in the DRC, Mozambique, South Africa, Zambia and Tanzania in partnership with centers of science in industrialized countries. All these individuals were selected by their respective institutions as key staff with the ability and influence to improve the safety and quality control of their laboratories and institutions. The participants (*pictured above with the NBTC's Dr. Sophie Brocard*) were very engaged throughout the training often asking questions and posing scenarios.

- **Biocontainment Engineering Working Group, International Federation of Biosafety Associations (IFBA).**

Mr. Miguel Grimaldo, a GNL biocontainment engineer with the training center, participated in the development of risk-management based guidelines for biocontainment laboratories as a member of the Biocontainment Engineering Working Group of the International Federation of Biosafety Associations (IFBA). These guidelines will eventually be endorsed by international organizations such as World Health Organization

(WHO), the Food and Agriculture Organization of the United Nations (FAO) and the Office International des Epizooties (OIE) the World Organization for Animal Health.

- **American Biological Safety Association.** During pre- and post-conference sessions of 2012 American Biological Safety Association (ABSA) conference held in Orlando, Florida in October, Mr. Grimaldo participated on following activities:

- He represented the NBTC as an Observer Member of the International Federation of Biosafety Associations. As such, Mr. Grimaldo participated on the 2012 ABSA International Forum on Sharing Biorisk Management Success Stories. During this forum, individual discussions were held with participants regarding training opportunities on Biosafety and Laboratory Biocontainment and Maintenance Operations.
- As member of the Biocontainment Engineering Working Group (BEWG) of the International Federation of Biosafety Associations (IFBA), Mr. Grimaldo participated in a follow-up meeting to the plenary meeting held in South Africa in June 2012. The topics of discussion included the priority items that were identified during the meeting in South Africa, as well as the IFBA Biocontainment Working Group requirement to create a "network of biocontainment engineers" capable of mentoring and supporting those new to the field; and the development of technical guidance for risk-based solutions to containment facilities and equipment. Creating such a network has been a goal of our NBTC since its inception. It is expected that the next members' meeting of the IFBA and the BEWG will take place during the preconference sessions of the Asian Pacific Biosafety Association 2013 conference to be held in Kuala Lumpur, Malaysia.
- Also during preconference of the 2012 ABSA Conference, Mr. Grimaldo participated a meeting to delineate key issues regarding the work-in-progress ANSI Z9.14 standard for the Testing and Performance Verification Methodologies for Ventilation Systems for BSL3 and ABSL3 Laboratories. The meeting included committee members attending the ABSA conference.

- **International Veterinary Biosafety Workgroup, South Africa.** In November,

Mr. Grimaldo participated in and presented at the 15th Workshop of the International Veterinary Biosafety Workgroup in Pretoria, South Africa. Mr. Grimaldo did a presentation on "Ventilation Control Modes and Failure Testing" (*pictured right*) as well as presented data and participated in a panel discussion about "Laboratory Pressurization during Fumigation". The meetings were held at the Agricultural Research Council of South Africa. The International Veterinary Biosafety Workgroup is made up of high and maximum containment facility safety officers and biocontainment engineers with the purpose of cross-training and the exchange of experiences in the operation of these types of laboratories. Mr. Grimaldo has been a



member of this working group since 1998; he has served as secretary of the group in the past and was elected representative for The Americas at this year's meeting.

### **Q3 highlights –**

- **Trainees from Victorian Infectious Disease Reference Laboratory in North Melbourne, Australia.** Collaboration is often the key to effective biosafety. During this reporting quarter two researchers from the Virus Identification Laboratory at the Victorian Infectious Disease Reference Laboratory in North Melbourne, Australia travelled to the NBTC in January 2013 for unique biosafety and biocontainment engineering discussions and training in advance of the opening of a new Australian BSL4 laboratory.

Drs. Julian Druce and Gina Papadakis' training included a review of the Galveston National Laboratory's biosafety requirements for BSL2, 3 and 4 as well as BSL4 facility training and BSL4 emergency procedures and incident response. Working with the NBTC's expert staff, Drs. Druce and Papadakis spent time engaged in the development of effective facility biosafety manuals and establishing BSL4 facility mechanical validation and re-verification practices. They received one-on-one instruction in BSL4 suit training, suit repairs and proper practices within the laboratory.

The training program was customized to the needs of the two researchers and included:

- A BSL4 Program overview.
- An overview of the BSL4 employee medical surveillance program.
- Instruction in Personal Protective Equipment (suit training, differences between Delta and Dover suits, options for gloves, etc.).
- Maintenance and repair of positive pressure suits.
- BSL4 facility operations and maintenance.
- General BSL4 laboratory procedures and oversight from a biosafety perspective.

The collaboration with researchers at the Victorian Infectious Disease Reference Laboratory will likely lead to the laboratory biocontainment engineers from Australia travelling to UTMB for extended discussions on BSL4 facility operations and review of training procedures. Updates, as applicable, will be provided in future reports.



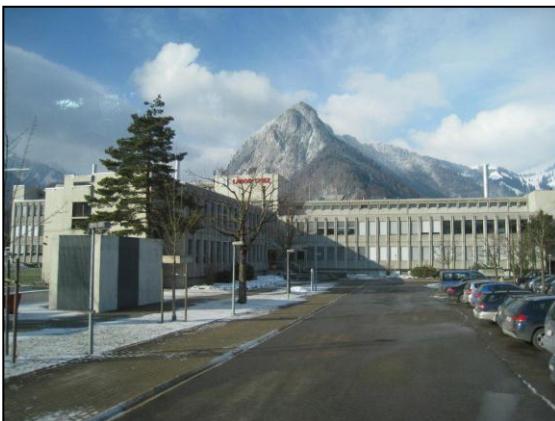


**Previous page left:** (l to r) GNL Biocontainment Engineer Miguel Grimaldo, BSL4 Trainer Corrie Ntiforo, Dr. Gina Papadakis, BSL4 Trainer Jet Newton, Dr. Julian Druce and GNL Director Dr. James LeDuc.

**Previous page right:** The group is pictured with engineers Miguel Grimaldo and John Carter during their biocontainment engineering tour.

**Left:** Drs. Druce and Papadakis receive BSL4 suit training from BSL4 instructor Jet Newton in the NBTC's mock laboratory.

- **Biocontainment Engineering Working Group, International Federation of Biosafety Associations (IFBA).** Continuing this quarter, Mr. Miguel Grimaldo, a GNL biocontainment engineer with the training center is participating in the development of risk-management based guidelines for biocontainment laboratories as a member of the Biocontainment Engineering Working Group (BEWG) of the International Federation of Biosafety Associations (IFBA). These guidelines will eventually be endorsed by international organizations such as World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO) and the Office International des Epizooties (OIE) the World Organization for Animal Health. Mr. Grimaldo has also been asked to take on a lead role for the “Promoting the BEWG Mentoring and Twinning Program.” This program is designed to identify and train biocontainment engineering personnel/key individuals in underdeveloped countries – i.e. “train the trainers,” something that our NBTC has been implementing since its inception.
- **Meeting of the European Research Infrastructure on Highly Pathogenic Agents.** Biocontainment Engineer and NBTC trainer Mr. Miguel Grimaldo was invited to the workshop of the European Research Infrastructure on Highly Pathogenic Agents (ERINHA) project held in Spiez, Switzerland in March of 2013. This activity was an international expert workshop on estimating construction and operational costs of BSL-4 laboratories. Mr. Grimaldo provided a presentation on *BSL4 Technical Specifications - "an American Perspective"* (pictured below). This invitation-only workshop was attended by an international audience of containment experts (facility managers, scientists, architects and engineers) from France, Germany, Italy, Netherlands, Austria, United Kingdom, Denmark, Greece, Spain and the U.S.



#### **Q4 highlights –**

- **Trainees from the Technical University of Denmark's National Veterinary Institute in Kalvehave, Denmark and from The Pirbright Institute in Surrey, United Kingdom.** In continued efforts toward collaboration on effective biosafety with our laboratory colleagues around the world, in Q4 two researchers travelled to UTMB's Galveston National Laboratory for instruction with the NBTC's unique biosafety and biocontainment engineering discussions and training.

In May, Dr. Susan Helen Grogan from the Pirbright Institute in Surrey, United Kingdom and Dr. Lars Holm (*pictured right with trainers Miguel Grimaldo and Dr. Tom Ksiazek*) from the National Veterinary Institute at the Technical University of Denmark participated in training much like Drs. Papadakis and Druce undertook in Q3. Their training included a review of the Galveston National Laboratory's biosafety requirements for BSL2, 3 and 4 as well as BSL4 facility training and BSL4 emergency procedures and incident response. Working with the NBTC's expert staff, Drs. Grogan and Holm spent time engaged in the development of effective facility biosafety manuals and establishing BSL4 facility mechanical validation and re-verification practices. They received one-on-one instruction in BSL4 suit training, suit repairs and proper practices within the laboratory.



The training program was customized to the needs of the two researchers and included:

- A BSL4 Program overview.
- An overview of the BSL4 employee medical surveillance program.
- Instruction in Personal Protective Equipment (suit training, differences between Delta and Dover suits, options for gloves, etc.).
- Maintenance and repair of positive pressure suits.
- BSL4 facility operations and maintenance.



- General BSL4 laboratory procedures and oversight from a biosafety perspective.
- **Pirbright Institute, United Kingdom.** In continued collaboration with the research team at the Pirbright Institute in Pirbright, England as they plan and progress toward the construction phases of their new animal research biocontainment facility, GNL attending veterinarian Dr. Curtis Klages visited the Institute this reporting quarter to provide in person veterinary consultation on a maximum level biocontainment facility in the Stage C design process. Dr. Klages provided experience-based insight on the operation of a maximum level biocontainment facility from a practical veterinary perspective, including animal flow (from initial entry to final disposition) , animal use protocols, animal containment levels, agents, decontamination techniques, protocol manipulation procedures, and other topics. He also offered future training opportunities either on the Pirbright campus proper or a “train the trainers” here on UTMB through the NBTC with follow on-training assistance at the Pirbright facility as the facility is being constructed and gets closer to validation (estimated to be 2016-2017). We will continue to provide guidance and insight into Stage D development which includes a more detailed review of the entire project as well as assist with the development of a BSL4 Biosafety program on site. The Biocontainment Resource Facility (BRF) will be the first fully positive pressure suited containment laboratory in England.
- **Wuhan University School of Medicine in China.** GNL Director and NBTC PI Dr. Jim LeDuc travelled to China to participate in the IXth Annual International Symposium on HFRS, HPS and Hantaviruses in Beijing and then traveled to Xi'an and Wuhan to meet with directors of the Chinese Centers for Disease Control provincial laboratories. While in Wuhan he met with the director of the Wuhan Institute of Virology, Chinese Academy of Sciences BSL4 laboratory now under construction near Wuhan. During his visit he toured the new facility, offered a presentation on the GNL and the NBTC to the new laboratory leadership team, and discussed topics of mutual interest in the design, operations and maintenance of a maximum biocontainment laboratory. Dr. LeDuc extended an open invitation for the Wuhan laboratory leadership team and staff to visit the GNL, and offered the opportunity for Chinese scientists, building engineers and biosafety officers to work closely with their counterparts in the GNL through the NBTC to build their own biosafety and biosecurity program. Sharing the lessons learned in



construction, commissioning and now operations of the GNL will be valuable for the Chinese team as they face problems similar to those already considered at the GNL. There was strong agreement regarding the need for rigorous biosafety and biosecurity programs to be in place at these maximum containment laboratories and mutual recognition of the global importance and critical, unique role played by the NBTC in offering a mechanism for sharing of techniques and experiences in the management and operations of these highly specialized laboratories.

***Aim 2. To provide the information and education necessary for a critical global discussion on the biosecurity, biosurety and related policy issues involved in the operation and maintenance of biocontainment facilities.***

**Background:** A significant unmet need exists on the part of students, staff and faculty for greater knowledge regarding the origin, development, necessity and implementation of national policies on the vital topics of biosecurity, biosurety and related policy issues that form the foundation for the safe and secure operation and maintenance of biocontainment facilities. We continue to address this need through our ongoing lecture series led by distinguished guest speakers in our “Topics in Biosecurity Symposia Series.” It is clear, however, that much more could be done to meet this aim; consequently, we are working to engage a number of national and international partners to educate audiences, to stimulate discussion, and to consider and propose solutions to our biosecurity and biosurety concerns. This effort includes, for example, participation in the ongoing efforts of the U.S. National Academy of Sciences and other organizations, and in other activities associated with the creation and operation of biocontainment facilities such as those in Central Asia, Asia, the Americas and in Africa. Our goal is to engage national and international leaders to develop and implement evidence-based policy discussions and eventual agreements that will enhance the security of biocontainment facilities around the world, including in those areas where little or no biosecurity infrastructure currently exists. This is being accomplished by participation in national, regional and international meetings and conferences and other outreach efforts, the facilitation of collaborative studies and investigations, the support of short- and long-term personnel exchanges to address specific goals in biosecurity, the development of programs suitable for a variety of educational methodologies, including ones that are web-based, and other timely opportunities designed to enhance global biosecurity.

**Progress:**

Progress during this past reporting year, highlighted by quarter (Q1, Q2, Q3, Q4), includes:

**Q1 highlights –**

- **International Working Group of the G-8.** GNL director, Dr. James LeDuc participated in the International Working Group of the G-8 workshop and roundtable discussion, “Science Collaboration and Security: Emerging CBRNCy Challenges and Threat Reduction Programs Beyond 2012” on September 13-14, 2012 hosted by the Landau Network Centro Volta in

Como, Italy. The meeting was also sponsored by the National Nuclear Security Administration (NNSA), Department of Energy. Dr. LeDuc was the key speaker in the session, “Evolving, Existing and New Threats Stemming from Nuclear/Radiological Sectors; Bio/Nano Sectors; Cyber and Information Technology Sectors and the implications for SE.” His talk focused on the emerging threats of synthetic biology and the expansion of biocontainment laboratories around the world, and recognized the need for a strong foundation in training in biosafety and biosecurity for personnel working in these facilities. Approximately 100 scientists, diplomats and political leaders from around the world participated in the conference.

## Q2 highlights –

- **International delegation from Turkey.** A delegation of international visitors from Turkey toured the GNL and learned about the NBTC during the reporting quarter. The delegation from the Turkish Chamber of Commerce (*pictured right*) visited the GNL in November and met with NBTC directors Dr. Jim LeDuc and Dr. Tom Ksiazek. The delegation also met with our NBTC fellow – Dr. Aysen Gargili – who is currently in residence in the GNL. Members of this delegation included Tarik Celik, Executive Director; Deniz Senyurt, Commercial Attaché, Consulate General of Turkey, Houston, plus Charlie Scott and Jacqueline Armstrong of BM&B Risk Management of Houston. Potential training and scientific collaborations were discussed.
- **University of Malaya in Malaysia.** A delegation from the University of Malaya also visited the GNL during this reporting quarter. The University of Malaya is Malaysia’s first and leading university and is located southwest of Kuala Lumpur. The University was designated as a Research University by the Malaysian government in 2006. The group’s visit to the Houston area was sponsored by the Malaysian Investment Development Authority and the Texas Medical Center – of which UTMB is a member. The group met with Dr. Ksiazek to tour the GNL and to learn more about the types of training opportunities offered through the NBTC, as well as potential areas for scientific collaboration.
- **U.S. Representative Pete Olson visits the NBTC.** In November the GNL and the NBTC were honored to host a visit by U.S. Representative Pete Olson. Congressman Olson represents Texas’ 22<sup>nd</sup> Congressional district in the U.S. House of Representatives and has been an enthusiastic backer of the NBTC since taking office in 2009. He, along with retiring U.S. Senator Kay Bailey Hutchison, has repeatedly and successfully sponsored efforts to garner federal support for the training program. This was the Congressman’s second visit to the GNL and his first to the NBTC. While on campus, he met with NBTC leadership and trainers



and toured the NBTC's biosafety training lab. During the tour he learned about the different safety techniques taught for research work at biosafety levels 2, 3 and 4 and he donned the corresponding personal protective equipment to get a feel for the unique aspects of biocontainment research.



Rep. Olson was presented with an appreciation plaque during his visit. Pictured are: (l to r) UTMB President Dr. David Callender, Dr. Tom Ksiazek, Dr. Sophie Brocard, Rep. Olson, Dr. Jim LeDuc, UTMB Provost Dr. Danny Jacobs and IHII Director Dr. Scott Weaver.



Rep. Olson also donned a BSL4 suit during his visit to the training center. Opportunities like this one, to expose national decision makers to the intricacies of biosafety and biosecurity, are invaluable to raising awareness of the need for such training.

- **Global Virus Network.** NBTC director Dr. Jim LeDuc participated in the semi-annual meeting of the Global Virus Network held in Baltimore in October. This was the fourth meeting since the GVN was established in 2011. Dr. LeDuc is a founding member of the group. At the meeting in Baltimore Dr. LeDuc was a featured speaker (*pictured right*) on the topic of the challenges in managing biosecure laboratories. He touted the NBTC program's training opportunities in biosafety and biocontainment engineering which could benefit countries that have recently opened new BSL3 and BSL4 facilities. Discussions are underway to offer NBTC training programs as an adjunct to other GVN training opportunities.



### **Q3 highlights –**

**Topics in Biosecurity Symposia Series.** This popular speaker series, typically reported on in our companion NBTC reports (Award Number W81XWH-09-2-0053, also titled National Biocontainment Training Center) included guests of international interest during this reporting quarter. A recap is listed below.

- **Dr. Malcolm Dando,** a professor of international security at the University of Bradford in the United Kingdom was the featured guest in the speaker series in February 2013. His presentation was entitled "*Biosecurity Education for Practicing Life Scientists: The Missing Past, Unsatisfactory Present and Uncertain Future.*" Dr. Dando spoke to a capacity crowd of researchers, safety professionals, students and community members. His remarks were well received and included discussion of future collaboration possibilities.





Dr. Dando is pictured right with GNL director and NBTC PI Dr. James W. Le Duc.

- **Joint US National Academy of Sciences—Indian National Academy of Sciences proposed symposium on biosafety and biosecurity of biocontainment laboratories.** Dr. LeDuc was part of a small delegation from the U.S. National Academy of Sciences that travel to India in January, 2013 to discuss with Indian colleagues from the Indian National Academy of Sciences a proposal to jointly host a bilateral meeting on laboratory biosafety and biosecurity tentatively scheduled to be held in India in the last quarter of CY13. The NBTC model of engagement in scientist-to-scientist training and mentoring and forging partnerships between the building engineers who manage the daily operations of these facilities will be discussed during the meeting.

#### Q4 highlights –

**Topics in Biosecurity Symposia Series continued.** In the current reporting quarter this popular speaker series hosted another international guest. In April, Dr. Patricia Nuttall from Oxford University visited the GNL and NBTC. A recap is listed below.

- The *Topics in Biosecurity* symposia series hosted by UTMB's Galveston National Lab and National Biocontainment Training Center hosted the twelfth session in their series in April featuring internationally esteemed arbovirologist **Dr. Patricia Nuttall**. This speaker series is aimed at assuring that UTMB faculty, staff, students and community members have maximum exposure to and participation in the ongoing federal discussion on biosecurity law, policy and application. These sessions continuously draw capacity crowds of faculty, students, staff and community members to hear from some of the world's leading experts on biosecurity. On April 18, Dr. Nuttall presented a session entitled "The Role of the Health Protection Agency in Homeland Defense for the United Kingdom." Dr. Nuttall was recently named a professor at Oxford University. Prior to her faculty appoint she served as the director of the Centre for Ecology & Hydrology with the United Kingdom's Natural Environment Research Council. Dr. Nuttall's research interests are in viruses transmitted by ticks and how tick saliva promotes virus transmission. During her stay at UTMB, Dr. Nuttall had the opportunity to meet with several UTMB researchers who are engaged in groundbreaking studies involving ticks and

virus transmission. UTMB is home to some of the world's only known research studies involving highly pathogenic tick-borne virus diseases under maximum biocontainment conditions.

# Topics in Biosecurity Symposia Series

The Galveston National Laboratory presents the next session in our symposia series featuring experts at the forefront of biosecurity policy development and implementation.

As the only active BSL4 research program underway on a U.S. academic campus, we seek to ensure that our students, staff and faculty have maximum exposure to and participation in this ongoing discussion.

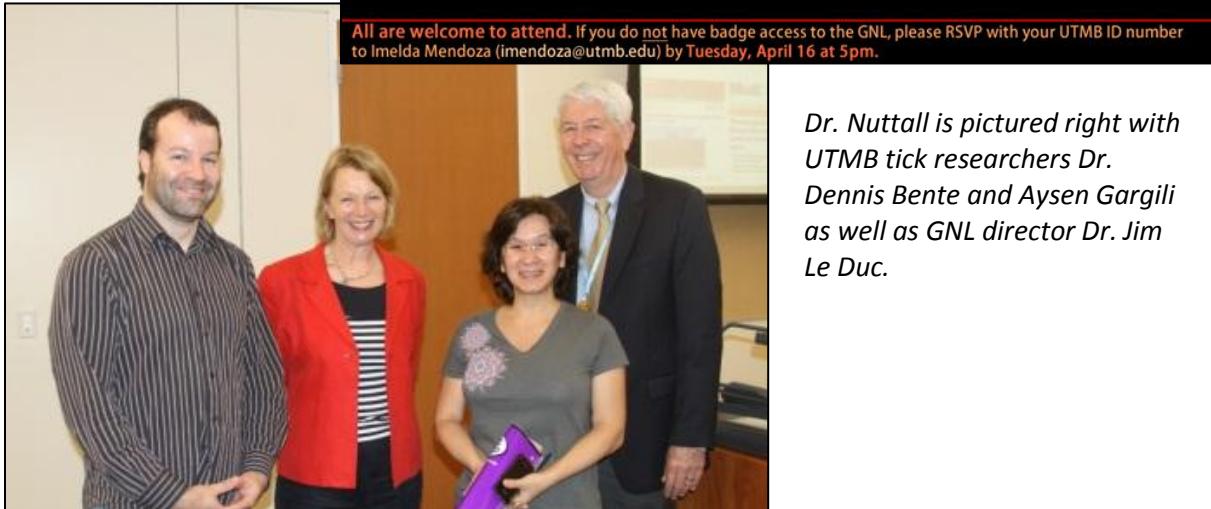
**Session XII**

**The Role of the Health Protection Agency in Homeland Defense for the United Kingdom**

**\*New Time\*** Thursday, April 18, 2013  
9:00 am, GNL 1st flr conference rooms

Featuring special guest:  
**Dr. Patricia Nuttall**

Professor of Arbovirology, Zoology Department, Oxford University, United Kingdom. Formerly with the Natural Environment Research Council as Director of the Centre for Ecology & Hydrology, Dr. Nuttall's research interests are in viruses transmitted by ticks and how tick saliva promotes virus transmission.



All are welcome to attend. If you do not have badge access to the GNL, please RSVP with your UTMB ID number to Imelda Mendoza ([imendoza@utmb.edu](mailto:imendoza@utmb.edu)) by Tuesday, April 16 at 5pm.

Dr. Nuttall is pictured right with UTMB tick researchers Dr. Dennis Bente and Aysen Gargili as well as GNL director Dr. Jim Le Duc.

- **U.S. Representative Randy Weber visits the GNL/NBTC.** In April 2013 the GNL and the NBTC were honored to host a visit by U.S. Representative Randy Weber and several members of his Congressional office administrative and legislative team. Congressman Weber (pictured right with Dr. Tom Ksiazek) represents Texas' 14<sup>th</sup> Congressional district in the U.S. House of Representatives which includes Galveston



Island where UTMB (including the GNL and NBTC) is located. He was elected to the House in 2012 and this was his first visit to the GNL/NBTC in early April. He currently serves as a member of the Foreign Affairs and the Science, Space, and Technology Committees which provide him with a unique perspective and influence into the research work done in the GNL and the need for well-trained lab personnel both domestically and in labs around the world. Rep. Weber and his staff (*pictured right with Drs. Jim LeDuc, Scott Weaver and Tom Ksiazek*) spent time with many of our researchers, engineers and biosafety trainers during their visit.



***Aim 3. To develop and implement a dedicated program to facilitate the establishment, maintenance and administrative oversight of operations of biocontainment facilities.***

**Background:** There are unique requirements for the operations of a biocontainment facility that extend beyond the scientific investigations and the safety and security infrastructure. For facilities such as the regional and national biocontainment laboratories constructed with support from NIH, as well as the independent commercial and not-for-profit institutions and foundations that manage biocontainment facilities and the international containment laboratories such as those now under construction in Central Asia under U.S. Department of Defense support, there is a need for a specialized administrative structure and culture. This culture must be sensitive and responsive to local needs and also address the unique operational challenges associated with the conduct of research and development involving highly dangerous infectious pathogens and the specialized business practices that are critical to sustaining the enterprise. These challenges are especially difficult ones that vary by organization with no standard model fully appropriate for all facilities.

There are some general principles that must be followed; however, in many instances the operational environment at each facility is unique and demands specialized attention. We captured these lessons learned as we brought the GNL online and embarked on the full operation of this national resource. We have developed plans to offer short and longer term training opportunities to administrative staff and institutional leadership of containment laboratories, as well as to students interested in careers in this field. Longer term fellowships are being established to provide relevant hands-on experience to the next generation of the biocontainment industry leaders. We have also created a standardized checklist of essential

tools, skills and procedures that are critical to the safe and secure operations of a biocontainment laboratory. This includes best business practices to ensure fiscal stability in the face of the high costs of security, utilities and specialized equipment required for successful operations.

### **Progress:**

Progress during this past reporting year, highlighted by quarter (Q1, Q2, Q3, Q4), includes:

#### **Q1 highlights –**

- We continue to host an emerging leader in biocontainment sciences from Turkey as a scientific fellow working in the GNL to gain experience in the conduct and direction of a modern biocontainment laboratory. Upon her return to Turkey next year, Dr. Gargili will direct a national biocontainment facility outside Istanbul. As an update to the report on Dr. Gargili's work provided in previous reports, during this reporting quarter Dr. Gargili completed her mentoring in BSL3 and accumulated all forty hours necessary to work independently in BSL3. Subsequently, she started her BSL4 training and has already completed the facility and suit training. Dr. Gargili had her first BSL4 entry a month ago and has already accumulated ten entries with over thirty hours thus far. At ACL-2, we made tremendous progress by adding more exotic tick vector species colonies. Dr. Gargili developed and improved the infestation techniques that we will use for animal infestations in ACL-4/BSL4. In the meantime the ACL-4 has been setup and work will commence in the next couple of weeks. Our progress was already presented as a talk at the NIAID/NIH sponsored MENA meeting in Istanbul in June and at the recent FP-7 Arbozoonet meeting in Orvieto, Italy as a poster presentation. Additionally, Dr. Gargili initiated a collaboration with Dr. Massoud Motamedei in the GNL Imaging Core facility to develop real-time live imaging capabilities in live ticks/animals, which will be employed in BSL4 for the visualization of the virus in the vector and the host. Dr. Gargili's goals for the next term are to complete her BSL4 training and work independently in the BSL4 as well as start the tick transmission studies in the ACL-4/BSL4.

#### **Q2 highlights –**

- We continue to host an emerging leader in biocontainment sciences from Turkey as a scientific fellow working in the GNL to gain experience in the conduct and direction of a modern biocontainment laboratory. As an update to the report on Dr. Gargili's work provided in previous reports, during this reporting quarter we are enthusiastic to note that Dr. Gargili conducted the first tick transmission study at BSL4 in November. We are the first BSL4 facility, at this point in time, which can conduct studies like this. Leading up to the experiment, Dr. Gargili, and her mentor, Dr. Dennis Bente, invested a great amount of work setting up the insectary room in the BSL4 as well as refining the techniques required to do the study. During the last three months, Dr. Gargili also accumulated further entries and hours in the BSL4 and should be granted independent access early in 2013. The collaboration with the GNL's Imaging Service Division has been intensified and we made some very valuable progress on

the real-time imaging techniques of ticks. We will conduct our first infectious studies within the next few weeks and expect some ground breaking results. Our efforts have been noticed by the scientific community, and we have been invited by two different journals to report our results. During this reporting quarter, Dr. Gargili also had the opportunity to meet with U.S. Representative Pete Olsen during his visit to the training center as well as with a delegation of Texas Turkish- American Chamber of Commerce.

- Also during the Q2 reporting quarter, Mr. Grimaldo returned to Argentina to continue biocontainment engineering training with the engineering and maintenance team at the Instituto Nacional de Enfermedades Virales Humanas “Dr. Julio Maiztegui” (INEVH) and the Universidad Technologica Nacional, both located in Argentina. In November, Mr. Grimaldo traveled to Argentina with three goals in mind: to continue the collaboration with the INEVH Laboratory in Pergamino, to expand outreach to other government laboratories doing infectious disease research that may benefit from training, and to participate as a speaker in the 3rd workshop of the IberoAmerican Biosafety Group. The visit to the INEVH laboratory continued the training/collaboration with the INEVH laboratory in Pergamino for the startup of their newly constructed BSL3 Laboratory (*Mr. Grimaldo is pictured above with the lab’s engineers*). Technicians from their facility have participated in our training programs in Galveston (2011) and we have provided training at their facility as well (2012). The INEVH Laboratory produces the vaccine for the Junín virus called Candid 1. Mr. Grimaldo also visited the BSL3 Laboratory (UOCCB) at the Malbran Institute in Buenos Aires and met with the laboratory director, biosafety officers and biocontainment maintenance staff. During his visit, he also received a tour and overview of the facility and the operations in Buenos Aires. Mr. Grimaldo also discussed the work carried out in the BSL3 Laboratory to identify training needs and to talk about the training opportunities available for the Malbran Institute staff onsite at the NBTC at UTMB. Lab director Dr. Alexis Edelstein is planning to participate in the NBTC’s BSL3 Biosafety Training Program in the spring of 2013, along with one of their safety staff. Also during this trip to



Argentina, Mr. Grimaldo actively participated as Biocontainment Expert and Speaker at the 3rd Workshop about Biosafety and Biocontainment on Animal Health of the IberoAmerican Biosafety Group (*pictured above*). Mr. Grimaldo presented the topic "Critical Elements of a Biocontainment Installation" and answered biocontainment requirement questions as part of a panel discussion. The meeting was held at the newly constructed Foot and Mouth Disease Diagnostic Laboratory of the National Secretariat of Animal Health (SENASA) in Buenos Aires.

### **Q3 highlights –**

- We continue to host an emerging leader in biocontainment sciences from Turkey as a scientific fellow working in the GNL to gain experience in the conduct and direction of a modern biocontainment laboratory. During this reporting quarter we were enthusiastic to report that Dr. Gargili accumulated the necessary entries and hours in the BSL4 and has qualified for independent access. She and her team of researchers began infectious studies with the establishment of an infected tick colony in BSL4. To our knowledge, this is the only such work being conducted at BSL4 in the country and potentially the world. Dr. Gargili and her colleagues also designed further infectious studies for the visualization of the virus either in the tick or in infected animals with real-time imaging techniques. They accumulated critical data on the imaging techniques in live ticks/animals and started to use them in BSL4 for the visualization of the virus in the vector and the host. Her team also collaborated with UTMB researcher Dr. Gustavo Valbuena's team and began to infest humanized mice with infected ticks in BSL4 to see the preliminary results of the infection on human skin. During this reporting period Dr. Gargili also provided mentorship to a visiting scientist (Dr. Adil elKhidir Bala) from Sudan for identification, artificial feeding and dissection techniques for the ticks. We are proud to have the opportunity to mentor the next generation of scientists that will undertake this groundbreaking research.



*Dr. Gargili is pictured right discussing her research work with UTMB constituents at a university-wide meeting.*

### **Q4 highlights –**

- Dr. Gargili completed her BSL4 training during the current reporting quarter and she was signed off on for independent access to the laboratory. She is *pictured right* accepting her fellowship completion



certificates from Dr. Jim LeDuc, Dr. Dennis Bente and Dr. Saravanan Thangamani. She and Dr. Bente's research team completed quite a number of experiments together during Dr. Gargili's eighteen months as an NBTC fellow. She also spent time in biocontainment facility training Miguel Grimaldo and his team and learned the engineering ins and outs of the BSL4 as well as the biosafety cabinets. Dr. Gargili recently returned to Turkey where she will use the knowledge learned while in residence as an NBTC fellow in the establishment and management of a BSL4 facility in her home country. She and Dr. Bente also submitted a manuscript to for publication describing much of the work that Dr. Gargili did while a fellow here. The manuscript is entitled "Influence of laboratory animal hosts on the life cycle of *Hyalomma marginatum* and implications for an in vivo feeding model for Crimean-Congo hemorrhagic fever virus." It was submitted to *Frontiers in Cellular and Infection Microbiology*, a new open access journal. It will be part of a special upcoming issue with the title "The biology and ecology of ticks shape the potential for the transmission of zoonotic pathogens."

***Aim 4. To develop and implement training opportunities that focus on the safe and secure operations of novel laboratory instrumentation being introduced into the biocontainment laboratory environment.***

**Background:** The rate of change in laboratory instrumentation and adaptation of novel technologies to the laboratory setting is progressing rapidly. Routine laboratory procedures are becoming more and more automated, saving technicians and investigators time and effort. Technologies that once were so costly as to limit their use to only a few facilities are now affordable for many laboratories. For example, the sequencing of a pathogen or host that once required months or even years of specialized investigation and costly outsourcing, now can be provided in a matter of hours through the use of automated, high throughput instruments never before available to the research community.

As these modern advances make their way into biocontainment laboratories where highly dangerous pathogens are studied, it is not always clear what safety concerns might exist. For instance, many automated pieces of equipment such as flow cytometry include procedures that could generate an infectious aerosol during wash steps or other routine operations, which might place laboratory workers at risk of accidental infection if appropriate precautions are not utilized. Decontamination of such instrumentation for service and maintenance is another major challenge. In addition, modern imaging equipment is now finding greater application within the research community. Both *in vivo* and *in vitro* imaging techniques and equipment are becoming available for use within the biocontainment laboratory environment for use in pathogenesis studies involving live animals or cell cultures infected with especially dangerous agents. Further, it is now possible to grow relatively large volumes of pathogens using modern bioreactor technology. The development of safe operating procedures, guidelines for product processing, and training on the safe use of each piece of equipment necessary for the production, processing and storage of the resultant product is required. There is an urgent need to develop well-validated procedures to safely and securely conduct these important studies while ensuring the safety of investigators and the surrounding environment.

Under this aim, we are focusing specifically on those processes that might generate infectious aerosols when live pathogens are investigated and on those instruments that will require decontamination prior to service by external personnel who may not be equipped to work in a biocontainment setting. A product of this effort will be the creation of detailed standard operating procedures to ensure the safe analysis of material originating from potentially infectious substances and the development of specialized safety interventions to be used to protect workers at all levels of biocontainment. Our efforts are focused on the BSL2 laboratories where the majority of this equipment is located and where the greatest number of users exists; however, we are also examining these resources when they are in use within BSL3 and BSL4 laboratories.

**Progress:** Demand for assistance under this Aim has been limited to internal GNL activities; consequently, our focus has evolved to the other Aims where it is clear that a substantial need exists.

**Aim 5. To develop and implement policies, procedures and training programs for the safe and secure conduct of preclinical studies to be undertaken within biocontainment at biosafety laboratory levels 2, 3 and 4 (BSL2, 3, 4) in compliance with the U.S. Food and Drug Administration(FDA) Good Laboratory Practice (GLP) regulations (21 CFR Part 58).**

**Background:** There is a growing requirement for the development of diagnostic tests, drugs and vaccines for use in the recognition, treatment and prevention of biological terrorism threats and emerging infectious disease agents. Bioterrorism threats are among the most dangerous infectious pathogens known to humankind, and their safe and secure handling must be done within the confines of specially constructed biocontainment laboratories. The level of biocontainment needed is specific to each particular pathogen and is layered from the lowest level, BSL2, to “high containment” found in BSL3 facilities, to “maximum containment” found only in BSL4 laboratories (highly complex facilities built with special air handling, waste sterilization and other safety and security protections incorporated into the physical plant and routine operations).

In order to be formally approved for use in humans, products developed for potential application in humans must be evaluated for safety and efficacy during preclinical studies using laboratory animals under safe conditions of biocontainment prior to undergoing clinical safety and efficacy testing in human clinical trials. In addition, in certain cases where efficacy testing in humans is logistically or ethically impractical, products may be approved under the FDA’s “Animal Rule” which allows for efficacy to be demonstrated in appropriate animal models. Preclinical safety and animal rule efficacy studies must be conducted by appropriately trained personnel under standardized conditions using well defined procedures and validated equipment as described in 21 CFR Part 58, commonly referred to as Good Laboratory Practices.

Each of these studies is likely to encompass activities across multiple levels of *in vitro* and animal biocontainment and, to date; few organizations have undertaken carefully regulated

studies on these highest threat pathogens. Processes and procedures needed for formal GLP studies in biocontainment have generally not been created or have not been tested in actual working biocontainment facilities.

### **Progress.**

Progress during this past reporting year, highlighted by quarter (Q1, Q2, Q3, Q4), includes:

#### **Q1 highlights –**

- We continued to prepare for support of GLP-compliant studies to be performed at BSL3 or BSL4 using laboratories in the GNL and elsewhere on the UTMB campus. The FDA requires that critical drugs and reagents are protected from potential mix-ups or contamination. We prepared standard operating procedures and associated equipment files for a dedicated regulatory studies support laboratory and general BSL2 laboratory, located on the 6<sup>th</sup> floor of the GNL. The dispensary laboratory is intended to provide a dedicated space for critical reagent (e.g. test and control articles) receipt, storage and handling and is equipped with a suite of basic laboratory equipment that has been validated according to a set of general operating parameters for storage and measurement of reagents. Likewise, a general BSL2 laboratory is being established for use on regulated (GLP) and other sponsored studies that require restricted access and/or segregation of laboratory work to meet compliance or contractual requirements. In addition to standard equipment consistent with other GNL BSL2 laboratories, this laboratory will house blood and clinical chemistry analyzers and a Tecan automated plate handling system. These lab spaces can be used to support studies in a GLP compliant manner and, when not in use for a compliant study, will be used to train facility personnel and validate potential test models and supporting procedures. GNL and UTMB personnel are continuing to develop standard operating procedures and associated documentation to support safe and secure future operations of those laboratories and to facilitate training of study personnel in appropriate performance and documentation of activities that would be performed in those dedicated laboratories. In addition, personnel are working with other GNL cores/divisions, UTMB Environmental Health and Safety, and individual investigators to develop specific procedures for quality assurance unit (QAU) oversight of studies performed in high biocontainment laboratories at UTMB and for validation of significant laboratory equipment, methodologies and information systems infrastructure that may be used in support of future product development-related studies in compliance with FDA regulations for product licensure. This is a long process that will require significant investments of time and effort to develop the robust program needed to ensure successful regulated studies conducted under biocontainment conditions. In the upcoming quarter, the GNL Regulatory Compliance Core and UTMB's Institutional Office of Regulated Nonclinical Studies will be hosting a workshop titled "***Ensuring the quality and integrity of animal model and efficacy studies at BSL4***". This workshop will be held in the GNL on the UTMB campus on Thursday and Friday, October 25-26, 2012 and will feature speakers from the U.S. Food and Drug Administration Medical Countermeasures Initiative, the National Institutes of Health's National Institute of Allergy and Infectious Diseases Office of Biodefense Research Affairs, the Biomedical Advanced Research and Development Authority's Division of

CBRN Countermeasures, and the U.S. Department of Defense Joint Project Manager - Transformational Medical Technologies. NBTC personnel will participate in this meeting and an update will be provided in a future quarterly report.

## **Q2 highlights –**

- The Institutional Office of Regulated Nonclinical Studies (ORNcS) along with the GNL Regulatory Compliance Core (GNL RCC) hosted a workshop titled "***Ensuring the quality and integrity of animal model and efficacy studies at BSL4***" on October 25-26, 2012. More than eighty onsite participants were from external organizations, including FDA, DoD, BARDA, NIH, U.S. BSL4 facilities, NIH-funded Regional Biocontainment Laboratories, Contract Research Organizations (CRO), and equipment vendor companies. Over twenty people participated remotely via video/teleconference. Goals of the workshop were to: 1) identify and discuss the challenges of applying Good Laboratory Practice (GLP) standards to ensure data integrity and quality in a maximum containment setting and assess when applying GLP standards is not feasible or appropriate; and 2) seek consensus on high-risk areas that potentially impact data quality and integrity in maximum containment, and explore potential options for implementing practices that will address them. The FDA and UTMB are collaborating to design and implement a training program to cross educate sponsors, scientists, veterinarians, quality assurance personnel, regulators, reviewers, and policy-makers to enable the conduct of regulated studies in ABSL3/4 in support of product approval via The Animal Rule. Key discussion topics and areas of concern identified during the October workshop were summarized and reviewed for incorporation into the curriculum of a week-long training program on GLP in Maximum Containment that is being jointly developed by UTMB and the Office of Counterterrorism and Emerging Threats (OCET) in the Office of the Chief Scientist at FDA. The pilot course is scheduled to occur April 1-5, 2013 in the GNL. Future progress reports will further detail this meeting and its outcome. ORNcS along with the GNL RCC continues to develop elements of an overall GNL facility quality system needed to support GLP-compliant studies. Generation of standardized operating procedures (SOPs) continues for the care and use of basic laboratory equipment and scientific activities conducted in a segregated GNL BSL2 regulatory laboratory. Faculty and staff from ORNcS and RCC are integrating efforts to plan projects prospectively to include quality systems in order to meet the increasing demand for conduct of regulated studies requiring the application of the principles of the GLP regulations. The independent Quality Assurance Unit (QAU) is developing an audit schedule to inspect GNL facility-based activities such as the BSL2 regulatory laboratory, the dispensary laboratory, information technology, animal resource activities, environmental monitoring, etc. The establishment of routine inspections helps assure that quality systems are maintained.

## **Q3 highlights –**

- The FDA and UTMB collaborated to design and implement a training program to cross educate sponsors, scientists, veterinarians, quality assurance personnel, regulators, reviewers, and policy-makers to enable the conduct of regulated studies in ABSL3/4 in

support of product approval via The Animal Rule. Key discussion topics and areas of concern identified during an October 2012 workshop were summarized and reviewed for incorporation into the curriculum of a week-long training program on the conduct of regulated studies in Maximum Containment. The course was jointly developed by UTMB and the Office of Counterterrorism and Emerging Threats (OCET) in the Office of the Chief Scientist at FDA. The pilot course occurred April 1-5, 2013 in the GNL. The next quarterly progress report will provide further detail this meeting and its outcome. The UTMB Office of Regulated Non-clinical Studies (ORNcS) along with the GNL Regulatory Compliance Core (RCC) continues to develop elements of an overall GNL facility quality system needed to support GLP-compliant studies. Generation of standardized operating procedures (SOPs) continues for the care and use of basic laboratory equipment and scientific activities conducted in a segregated GNL BSL2 regulatory laboratory. Faculty and staff from ORNcS and RCC are integrating efforts to plan projects prospectively to include quality systems in order to meet the increasing demand for conduct of regulated studies requiring the application of the principles of the GLP regulations. The independent Quality Assurance Unit (QAU) is developing an audit schedule to inspect GNL facility-based activities such as the BSL2 regulatory laboratory, the dispensary laboratory, information technology, animal resource activities, environmental monitoring, etc. The establishment of routine inspections helps assure that quality systems are maintained.

#### **Q4 highlights –**

- A pilot course entitled ***Achieving Data Quality and Integrity in Maximum Containment Laboratories*** was held this quarter (April 1-5, 2013) in the Galveston National Lab. Developed as a collaborative project between UTMB and the United States Food and Drug Administration (FDA), the training program included four days of instruction plus a half day of interactive mock-BSL4 laboratory exercises in UTMB's National Biocontainment Training Center. The primary course objective was to cross educate sponsors, scientists, veterinarians, quality assurance personnel, regulators, Agency reviewers, and Agency policy-makers to enable the conduct of regulated studies in support of product approval via FDA's Animal Rule. For many Agency reviewers and Sponsor Contracting Officers, the laboratory exercise was a rare opportunity to experience physical restrictions due to biosafety requirements. Sixty-nine attendees participated in the course, including FDA representatives from the Centers for Drugs, Biologics, and Veterinary Medicine, the Office of Regulatory Affairs, and the Office of Counterterrorism and Emerging Threats. Faculty and attendees included members from the Center for Disease



Control and Prevention, Department of Army Inspector General Battelle, US Army Medical Research Institute of Infectious Diseases, National Institute of Allergy and Infectious Diseases and the Health Protection Agency from Public Health England, United Kingdom. The ORNcS is currently reviewing course evaluations; initial course feedback from FDA and course attendees is very positive. The training program also included development of an online Basic GLP course. Prior to launch, course materials were reviewed by subject matter experts within the FDA. Course funding was awarded through a collaborative educational grant with the FDA. The first year of the five-year grant required the development and implementation of the pilot training program. Presentations summarizing the historic event were given at UT Health Medical School Academy of Master Educators/UTMB Academy of Master Teachers Educational Symposium in Houston, TX; U.S. FDA Medical Countermeasures Initiative Regulatory Science Symposium at FDA Headquarters in Silver Springs, MD; 5th Annual NBL-RBL Network Meeting (Directors Meeting) at UTMB; and the 11th Annual Emerging Infectious Diseases plus Biodefense Vaccines, Therapeutics and Diagnostics, in Washington, D.C. Due to Federal budget sequestration, potential East coast sites for the 2014 course are in discussion. In preparation, site visits to other BSL4 laboratories occurred in June. UTMB and FDA faculty toured the National Biodefense Analysis and Countermeasures Center, the new United States Army Medical Research Institute of Infectious Diseases (USAMRIID) BSL3/4 laboratory, the National Institute of Allergy and Infectious Diseases (NIAID) Integrated Research Facility (IRF), and the National Institute of Health (NIH) BSL4 training laboratory. The Institutional Office of Regulated Nonclinical Studies (ORNcS) is currently in the process of recruiting a second Study Director to increase GNL's capability to conduct studies for the advancement of medical countermeasures. The Quality Assurance Unit conducted a data audit of animal records in order to assist GNL's Senior Biocontainment veterinarian in the development of standardized data capture processes.



**Key Research Accomplishments.** Significant progress has been made in addressing each of the Aims identified for study, with the exception of Aim 4, that deals with safety precautions of modern laboratory equipment. The level of international engagement with laboratory scientists and biosafety officers around the world has been exceptional and clearly demonstrates a substantial demand for the training we are offering. We have been especially gratified by the warm reception and very positive comments that we have received from our colleagues dealing with biocontainment building maintenance and operations. This is a critically important link in the continued safe and secure operations of biocontainment laboratories, yet there is virtually no international source of guidance or established best practices. We are proud to be at the forefront of addressing this need.

**Reportable Outcomes.** Important partnerships and exchanges have been established both with international biosafety associations and with the individual leadership of international biocontainment laboratories. Further, several individuals have benefited from extensive training on site at UTMB or at their home facility. These are significant steps towards developing leaders around the world and will serve as a foundation for future growth and dissemination of best practices to a much wider international audience.

**Conclusions.** The value of international engagement on a personal level cannot be overstated. The friendships and mutual respect that develops through our training efforts not only enhances the safe and secure operations of containment laboratories around the world, but it also fosters a culture of trust and transparency that directly enhances global security.